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NOTE

SYNTHESIS OF 2,6-DIMETHYLBENZAMIDE N-(5-METHYL-3-ISOXAZOLYL) (D2916) LABELLED WITH ^{14}C

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SUMMARY

Carbonation of 2,6-dimethyl phenyl lithium with $^{14}CO_2$ afforded 2,6-dimethylbenzoic acid, α-^{14}C **2** which was transformed into 2,6-dimethylbenzoic acid halide,α-^{14}C **3**. Subsequent condensation of the latter compound with 3-amino 5-methyl isoxazole afforded 2,6-dimethylbenzamide N-(5-methyl-3-isoxazolyl) (D2916) **4** (radiochemical 95% purity) in an overall yield of about 35% based on [^{14}C] barium carbonate

Key words: 2,6-dimethylbenzoic acid, α-^{14}C; 2,6-dimethylbenzoic acid halide,α-^{14}C; 2,6-dimethylbenzamide N-(5-methyl-3-isoxazolyl); (D2916).

INTRODUCTION

2,6-dimethyl N-(5-methyl-3-isoxazolyl) benzamide (D2916) (scheme.1) has been described as a new potent anticonvulsant exhibiting pharmacological properties similar to those of carbamazepine (1,2), as demonstrated by the maximal electroshock (MES) and subcutaneous pentylene tetrazole (sc PTZ) tests. Its toxicity is weak-neurologic deficits were observed in rat with doses up to 500 mg/kg.

In vitro studies with human liver micrososmes have shown that D2916 is rapidly hydroxylated to an active metabolite 2,6-dimethyl N-(5-hydroxymethyl-3-isoxazolyl) benzamide (D3187) (3). This metabolite was also observed in the plasma of rats given orally D2916 (4). A sex difference was shown in the rats towards the MES test, its anticonvulsant

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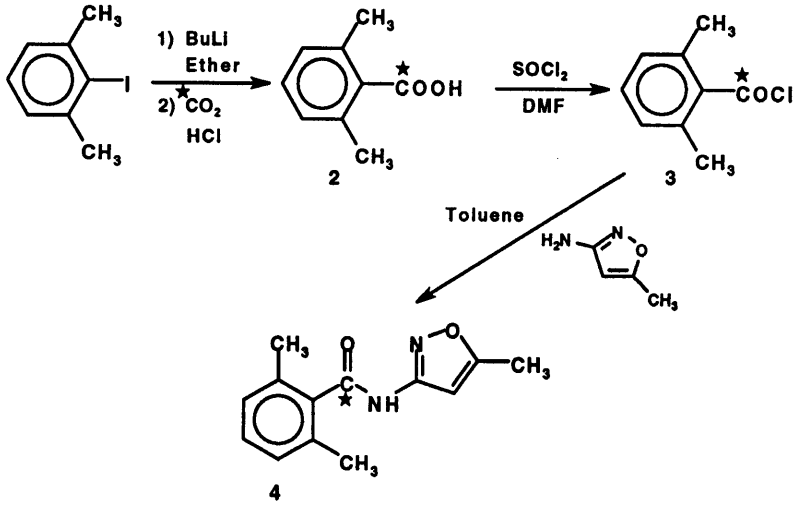
effect lasted longer in the female than in the male. This difference of activity between the two sexes could be due to a lower clearance of active metabolite in the female. In order to study the metabolic pathway of D2916 in male and female rats and to confirm this hypothesis (5), the latter was labelled with ^{14}C in the carbonyl group. This preparation was performed according to the reaction sequence depicted in scheme 1.

SYNTHESIS

The carbonation of 2,6-dimethyl phenyllithium with $^{14}CO_2$ (6) afforded 2,6-dimethylbenzoic acid ^{14}C **2** in 66% yield. The reaction of thionyl chloride (7) in the presence of dimethyl formamide led to 2,6-dimethylbenzoic acid halide ^{14}C **3** in 96% yield. Subsequent condensation of the latter compound with 3-amino 5-methyl isoxazol in toluene at 100°C (8) afforded 2,6-dimethylbenzamide N-(5-methyl-3-isoxazolyl) (D2916) **4** in 56%yield.



Scheme 1

EXPERIMENTAL

General comments. All starting organic chemicals were obtained from Aldrich chemical Co. The evaporation were performed under vacuum using a rotary evaporator. ^1H NMR spectra were recorded on a Bruker WB 200AM spectrometer. All ^1H chemical shifts are reported in part-per million down filed relative to tetramethylsilane (TMS) as internal

standard. Melting points (mp) were determined on an Electrothermal digital apparatus. Analytical thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 F 254, 0,2 mm thick) with both detection by ultra violet light at 254 nm and visualisation by iodine. Silica gel 60 (chromagel, 230-400 mesh, SDS) was used.

Radioactive samples were measured using. Packard 4550 scintillation counter.

1) 2,6-dimethylbenzoic acid,α-^{14}C 2

On a vacuum -manifold 987 mg (5.00 mmol, 50 mCi totally) of barium (^{14}C) carbonate were cautiously treated with 40 ml of concentrated sulphuric acid in order to obtain a slow liberation of (^{14}C) carbon dioxide. The (^{14}C) carbon dioxide was vacuum transferred into a liquid nitrogen cooled flask containing a degassed solution of 5.00 mmol of 2,6-dimethyl phenyl lithium in 40ml of dry ether. The carboxylation was carried out at 25°C for 20 hours. Then the reaction vessel was flushed with nitrogen, the reaction mixture was decomposed at -10°C by the slow addition of 20 ml of dilute hydrochloric acid, and the ether solution was washed with water and evaporated to dryness. The residue was taken up in sodium hydroxide (1N) solution and extracted with ether. The aqueous solution was concentrated to remove the organic solvents, then was acidified to precipitate the crude product, which was collected, washed with water and recrystallized from ether; yield 495 mg (3.30 mmol, 66%).

S.A. = 360 MBq/mmol, 10 mCi/mmol.

m.p = 114°C

IR (KBr) ν cm^{-1} 3200-2700 (OH); 1700-1650 (CO); 1600-1550 (CH_{Ar}).

^{1}H NMR (200MHz, $CDCl_3$): δ 7.30 ppm (q, 1H); 7.10 ppm (d, 2H); 2.45 ppm (s, 6H).

2) 2,6-dimethylbenzoic acid halide,α-^{14}C 3

To 495 mg (3.30 mmol) of acid **3** were added 2 drops of DMF , 5 ml of thionyl chloride, and the mixture was refluxed for 2 hours. The excess thionyl chloride was distilled off. The yield was 534 mg (3.17 mmol) 96% yield.

3) 2,6-dimethylbenzamide N-(5-methyl-3-isoxazolyl) (D2916) ^{14}C 4

To 534 mg (3.17 mmol) of 2,6-dimethylbenzoic acid halide ^{14}C 3 in toluene (50 ml) at 50°C were added 622 mg (6.34 mmol) of 3-amino5-methyl isoxazol. This mixture was heated at 100°C for 1 hour. The pure (D2916) ^{14}C 4 was obtained from silicagel column chromatography (95/5; methylene dichloride/ethanol) in 56% (408 mg, 1.77 mmol).

S.A. = 360 MBq/mmol, 10 mCi/mmol.

m.p = 185°C

IR (KBr) ν cm^{-1} 3300-3000 (NH); 1700-1660 (CO); 1650-1570 (CH_{Ar}); 1500-1450 (C-CH_3)

^1H NMR (200MHz, $CDCl_3$): δ 8.30 ppm (s, 1H); 7.22 ppm (t, 1H); 7.08 ppm (d, 2H); 6.69 (s,1H); 2.44 ppm (s,3H), 2.35 ppm (s, 6H).

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